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(57) Abstract

This invention relates to macrocyclic molecules which inhibit metalloproteinases, including aggrecanase, and the production of tumor necrosis factor (TNF). In particular, the compounds are inhibitors of metalloproteinases involved in tissue degradation and inhibitors of the release of tumor necrosis factor. The present invention also relates to pharmaceutical compositions comprising such compounds and to methods of using these compounds for the treatment of inflammatory diseases.

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TITLE

NOVEL MACROCYCLIC COMPOUNDS AS METALLOPROTEASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to macrocyclic molecules which inhibit metalloproteinases, including aggrecanase, and the production of tumor necrosis factor (TNF), pharmaceutical preparations containing them and to their use as pharmaceutical agents. In particular the compounds are inhibitors of metalloproteinases involved in tissue degradation and inhibitors of the release of tumor necrosis factor.

BACKGROUND OF THE INVENTION

There is now a body of evidence that metalloproteinases (MP) are important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as rheumatoid and osteoarthritis, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins and TIMP (tissue inhibitor of metalloproteinase), which form inactive complexes with the MP's.

Osteo- and rheumatoid arthritis (OA and RA respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. J. Bone Joint Surg. 52A, 1970, 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine,

aspartic and metalloproteinases. The available evidence supports that it is the metalloproteinases which are responsible for the degradation of the extracellular matrix of articullar cartillage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 and Ibid. 27, 1984, 305-312). In addition, aggrecanase (a newly identified metalloproteinase enzymatic activity) has been identified that provides the specific cleavage product of proteoglycan, found in RA and OA patients (Lohmander L.S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Therefore metalloproteinases (MP) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP inhibitors, and many compounds have been suggested for this purpose (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

This invention describes macrocyclic molecules that inhibit aggrecanase and other metalloproteinases. These novel molecules are provided as cartilage protecting therapeutics. The inhibiton of aggrecanase and other metalloproteinases by these novel molecules prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of osteo- and rheumatoid arthritis.

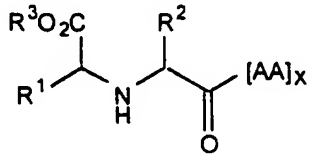
Tumor necrosis factor (TNF) is a cell associated cytokine that is processed from a 26kd precursor form to a 17kd active form. TNF has been shown to be a primary mediator in humans and in animals, of inflammation, fever, and acute phase responses, similar to those observed during acute infection and shock. Excess TNF has been shown to be lethal. There is now considerable evidence that blocking the effects of TNF with specific antibodies can be beneficial in a variety of circumsatnces including autoimmune diseases such as rheumatoid arthritis (Feldman et al, Lancet, 1994, 344, 1105) and non-insulin dependent diabetes melitus. (Lohmander L.S. et al. Arthritis Rheum. 36, 1993, 1214-22) and Crohn's disease (Macdonald T. et al. Clin. Exp. Immunol. 81, 1990, 301) .

Compounds which inhibit the production of TNF are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently it has been shown that a matrix metalloproteinase or family of metalloproteinases, hereafter known as TNF-convertases (TNF-C), as well as other MP's are capable of cleaving TNF from its inactive to active form (Gearing et al Nature, 1994, 370, 555). This invention describes macrocyclic molecules that inhibit this conversion and hence the secretion of active TNF-a from cells. These novel molecules provide a means of mechanism based therapeutic intervention for diseases including but not restricted to septic shock, haemodynamic shock, sepsis syndrom, post ischaemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancer, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, rheumatoid arthritis, multiple sclerosis, radiation damage, hyperoxic alveolar injury, HIV and non-insulin dependent diabetes melitus.

Since excessive TNF production has been noted in several disease conditions also charactarized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF production may also have a particular advantage in diseases where both mechansisms are involved.

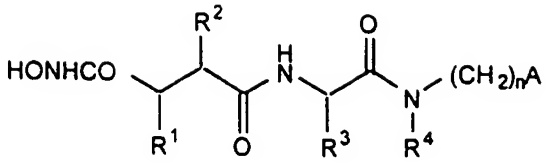
There are several patents which disclose hydroxamate and carboxylate based MMP inhibitors.

PCT International Publication No. WO 92/213260 describes N-carboxyalkylpeptidyl compounds of general formula:

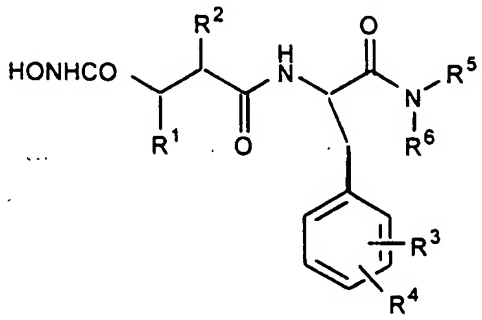


wherein AA is an amino acid, as inhibitors of matrix metallproteinase mediated diseases.

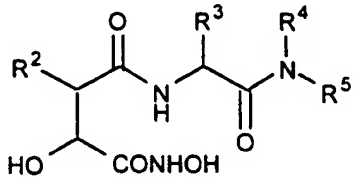
PCT International Publication No. WO 90/05716 discloses hydroxamic acid based collagenase inhibitors having the general formula:



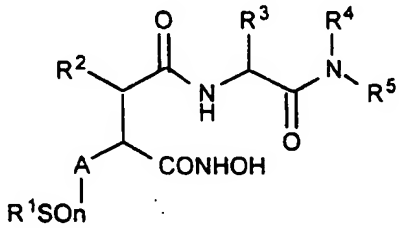
PCT International Publication No. WO 92/13831 describes related hydroxamic acids having collagenase inhibiting activity with the general formula:



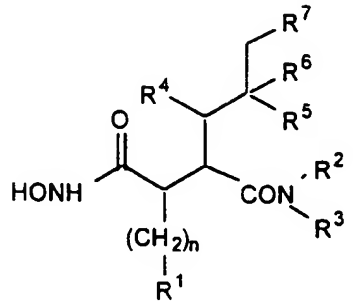
PCT International Publication No. WO 94/02446 discloses metalloproteinase inhibitors which are natural amino acid derivatives of general formula:



WO95/09841 describes compounds that are hydroxamic acid derivatives and are inhibitors of cytokine production.



European Patent Application Publication No. 574,758 A1, discloses hydroxamic acid derivatives as collagenase inhibitors having the general formula:



GB 2 268 934 A and WO 94/24140 claim hydroxamate inhibitors of MMPs as inhibitors of TNF production.

The compounds of the current invention act as inhibitors of MMPs, in particular aggrecanase and TNF-C, thereby preventing cartilage loss and destruction and inflammatory disorders involving TNF. The hydroxamic and carboxylic acids and derivatives are cyclic, and thus non-peptide in nature, which offers a distinct advantage over existing inhibitors because they have superior pharmacokinetic parameters. A selection of these molecules are water soluble and are orally bioavailable.

SUMMARY OF THE INVENTION

This invention provides novel hydroxamic acids and carboxylic acids (described below) which are useful as inhibitors of metalloproteinases, such as aggrecanase and TNF-C. The present invention also includes pharmaceutical compositions comprising such compounds and methods of using such compounds for the treatment of arthritis and other inflammatory disorders as described previously, in a patient.

Also included in the present invention are pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising a compound of the present invention (described below) for the treatment of arthritis and other inflammatory disorders as described previously.

The present invention also includes methods of inhibiting metalloproteinases, such as aggrecanase and TNF-C, and for the treatment of arthritis by administering a compound of the present invention in combination with one or more second therapeutic agents selected from other inhibitors of metalloproteinases, such as aggrecanase and TNF-C and/or therapeutic agents for the treatment of arthritis and inflammation.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides novel compounds which are useful as inhibitors of metalloproteinases, such as aggrecanase and TNF-C. The present invention also includes pharmaceutical compositions comprising such compounds and methods of using such compounds for the treatment of arthritis and other inflammatory disorders as described previously, in a patient.

Also included in the present invention are pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising a compound of the present invention, for the treatment of arthritis and other inflammatory disorders as described previously.

The present invention also includes methods of inhibiting metalloproteinases, such as aggrecanase and tumor necrosis factor alpha, and for the treatment of arthritis by administering a compound of the present invention in combination with one or more second therapeutic agents selected from other inhibitors of metalloproteinases, such as aggrecanase and tumor necrosis factor alpha and/or therapeutic agents for the treatment of arthritis and inflammation.

The compounds of the present invention include the following compounds, or a pharmaceutically acceptable salt or prodrug form thereof:

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine-n-pentyl ester]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-4-phenyl-1-butylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[5-methoxytryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[1-(2,5-dimethoxyphenyl)-2-glycine amidoethanol]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine-t-butyl ester]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid-a, g -di-t-butyl ester]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-2-phenyl-1-butylamide]-cyclopentadecane-13-N-hydroxycarboxamide

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(2-aminoethyl)-1-methylpyrrole]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(2-aminoethyl)benzenesulphonamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid-g-cyclohexyl ester-N-methyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-phenylalanine-p-fluoro-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-phenylalanine-p-methoxy-N-(*S*)-a-methylbenzylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-cyclohehylmethyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-3-phenyl-1-propyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-3,3-diphenylpropyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-(2-aminoethylamino)ethyl pyrrolidine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-3(2'-naphthyl)alanine-N-methyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[ethyl-4-amino-1-piperidine carboxylate]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[5-methyl tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-4-trifluoromethylbenzyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(diethylamino)ethyl-4-amino benzoate]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[6-fluorotryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[6-methoxy tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-methylpiperazinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-alanine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-valine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-tert-butylglycine-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(b-alanine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(ethoxycarbonyl-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-hydroxy-2-phenylethyl)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-benzylpiperazinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-phenylpiperazinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-(2-pyridyl)piperazinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(a-cyclopropaneethyloxycarboxamide-b-alanine)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[glycine-N-4-(1-piperidinyl)piperidinamide]carboxamide} cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(*R*-isopropyloxycarbonyl-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(*S*-isopropyloxycarbonyl-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-thiazole-4-acetic acid)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(a-cyclopropaneethyloxycarboxamide-b-alanine-N-dimethylamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(a-cyclopropaneethyloxycarboxamide-b-alanine-N-

morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-thiazole-4-acetyl-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-serine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-piperidinamide-3-carboxylic acid)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-2,6-dimethylmorpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-ethoxycarbonylpiperazinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-ethoxycarbonylpiperidinamide) carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[4-(1-morpholinyl)phenyl]carboxamide}cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[glycine-N-(4-(1-morpholinyl)anilide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-piperidinamide-4-carboxylic acid)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-methylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[alanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[methylcarboxy]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[glycine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-morpholinoethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-morpholinopropylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[pheylalanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[leucine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R,S)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-phenylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[t-butylglycine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-benzylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-(2-oxo-pyrrolidino)propylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-ethylpyrrolidinocarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-3-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-(1,1,1-trifluoroethyl)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-(2-pyridyl)ethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R,S-1-methyl -3-pheylpropyl)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-imidazoylpropylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[e-N-t-butyloxycarbonyllysine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[lysine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

22S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-N-morpholinocarboxyamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2(4-imidazoyl)ethylcarboxyamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-R-(2-R-hydroxyindane)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-S-(2-S-hydroxyindane)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-aminobenzylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-piperazinoethylcarboxamide]-cyclopentadecane-13-N-, hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-methylpiperinocarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-(2-R,S-methyl-piperidino)propylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(S)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[aspartate(O-t-butyl)-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[aspartate-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-azaphenylalanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-benzhydrylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide.

In the present invention it has been discovered that the compounds above are useful as inhibitors of metalloproteinases, including aggrecanase and TNF-C, and are useful for the treatment of rheumatoid arthritis, osteoarthritis and related inflammatory disorders, as described previously. These compounds inhibit the production of TNF in animal models and are useful for the treatment of diseases mediated by TNF.

The present invention also provides methods for the treatment of osteo- and rheumatoid arthritis and related disorders as described previously, by administering to a host a pharmaceutically or therapeutically effective or acceptable amount of a compound of the present invention as described above. By therapeutically effective amount, it is meant an

amount of a compound of the present invention effective to inhibit the target enzyme or to treat the symptoms of osteo- or rheumatoid arthritis or related disorder, in a host.

The compounds of the present invention can also be administered in combination with one or more additional therapeutic agents. Administration of the compounds of the present invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

By "therapeutically effective amount" it is meant an amount of a compound of the present invention that when administered alone or in combination with an additional therapeutic agent to a cell or mammal is effective to inhibit the target enzyme so as to prevent or ameliorate the inflamatory disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that a compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

By "stable compound" or "stable structure" is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds herein described may have asymmetric centers. Unless otherwise indicated, all chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. It will be appreciated that compounds of the present invention may contain asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. It is well known

in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

When a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring.

When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of the present invention then such substituent may be bonded via any atom in such substituent. For example, when the substituent is piperazinyl, piperidinyl, or tetrazolyl, unless specified otherwise, said piperazinyl, piperidinyl, tetrazolyl group may be bonded to the rest of the compound via any atom in such piperazinyl, piperidinyl, tetrazolyl group.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By stable compound or stable structure it is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "substituted", as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (for example, "C_1-C_{10}" denotes alkyl having 1 to 10 carbon atoms); in addition lower alkyl defines branched and/or unbranched alkyl chain of from 1 to 8 C atoms; "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)); "alkoxy" represents an alkyl group of indicated

number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or polycyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl; and "bicycloalkyl" is intended to include saturated bicyclic ring groups such as [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl and the like; and "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like.

"Alkylcarbonyl" is intended to include an alkyl group of an indicated number of carbon atoms attached through a carbonyl group to the residue of the compound at the designated location. "Alkylcarbonylamino" is intended to include an alkyl group of an indicated number of carbon atoms attached through a carbonyl group to an amino bridge, where the bridge is attached to the residue of the compound at the designated location. "Alkylcarbonyloxy" is intended to include an alkyl group of an indicated number of carbon atoms attached to a carbonyl group, where the carbonyl group is attached through an oxygen atom to the residue of the compound at the designated location.

The terms "alkylene", "alkenylene", "phenylene", and the like, refer to alkyl, alkenyl, and phenyl groups, respectively, which are connected by two bonds to the rest of the structure of the present invention-III. Such "alkylene", "alkenylene", "phenylene", and the like, may alternatively and equivalently be denoted herein as "-(alkyl)-", "-(alkyenyl)-" and "-(phenyl)-", and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of the present invention are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of the present invention wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention, phosphate esters, dimethylglycine esters, aminoalkylbenzyl esters, aminoalkyl esters and carboxyalkyl esters of alcohol and phenol functional groups in the compounds of the present invention and the like.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound of of the present invention is modified by making acid or base salts of the compound of the present invention. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids and the like.

The pharmaceutically acceptable salts of the compounds of the present invention include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of the present invention formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of the present invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of list with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

As discussed above, pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid, respectively, in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

SYNTHESIS

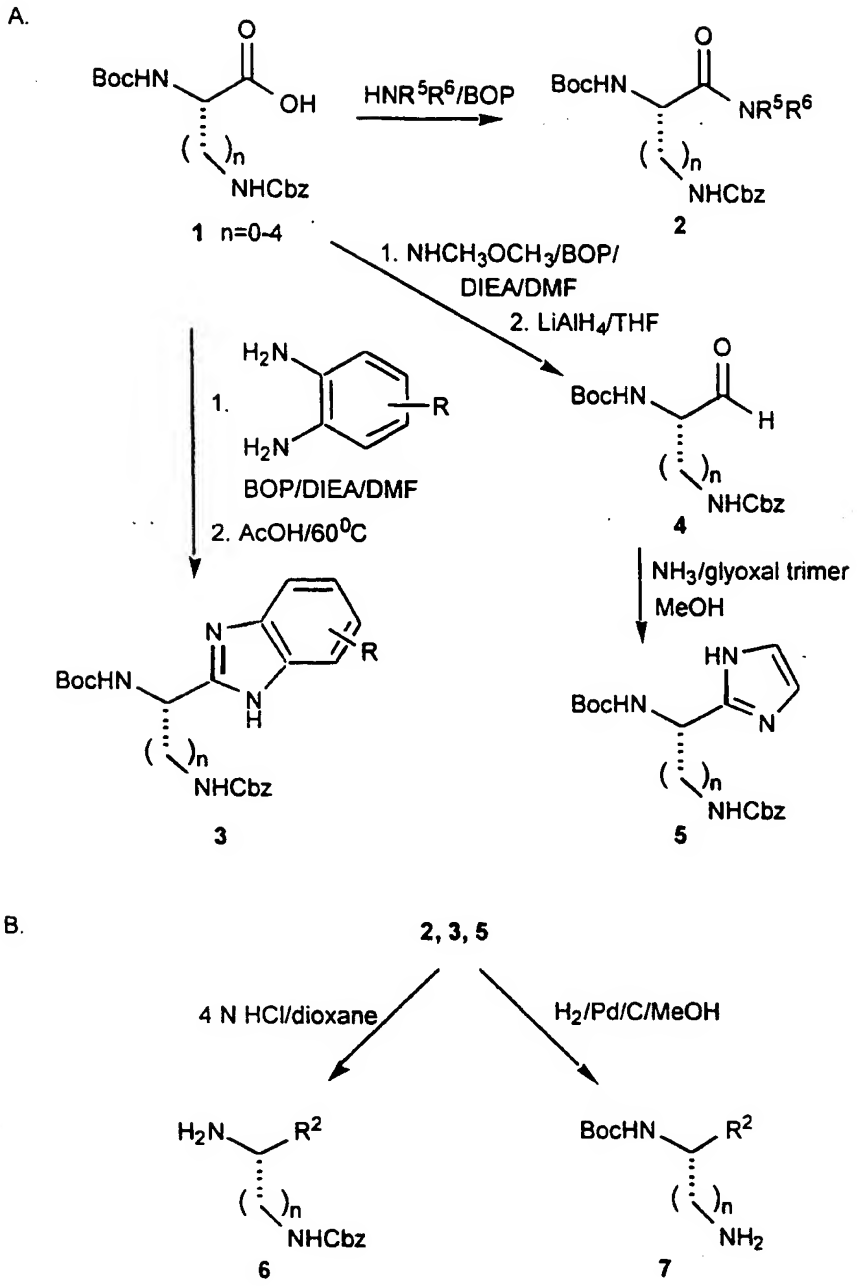
The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents

and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

The compounds of the present invention may be prepared by the methods outlined in the Schemes below. A diprotected 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, ornithine or lysine (compound 1, Scheme 1) is converted to its corresponding amide 2 using a coupling agent such as BOP. Coupling of 1 with a diaminobenzene followed by reaction in acetic acid at 60_ C produces a benzimidazole analog 3. 1 can also be converted to an aldehyde 4 which is reacted with ammonia and glyoxal trimer to give an imidazole analog 5. Deprotection of the Na-Boc group of 2, 3 and 5 using an acid such as 4 N HCl in dioxane gave compound 6. Removal of the side chain protecting group of 2, 3 and 5 using hydrogenation afforded compound 7.

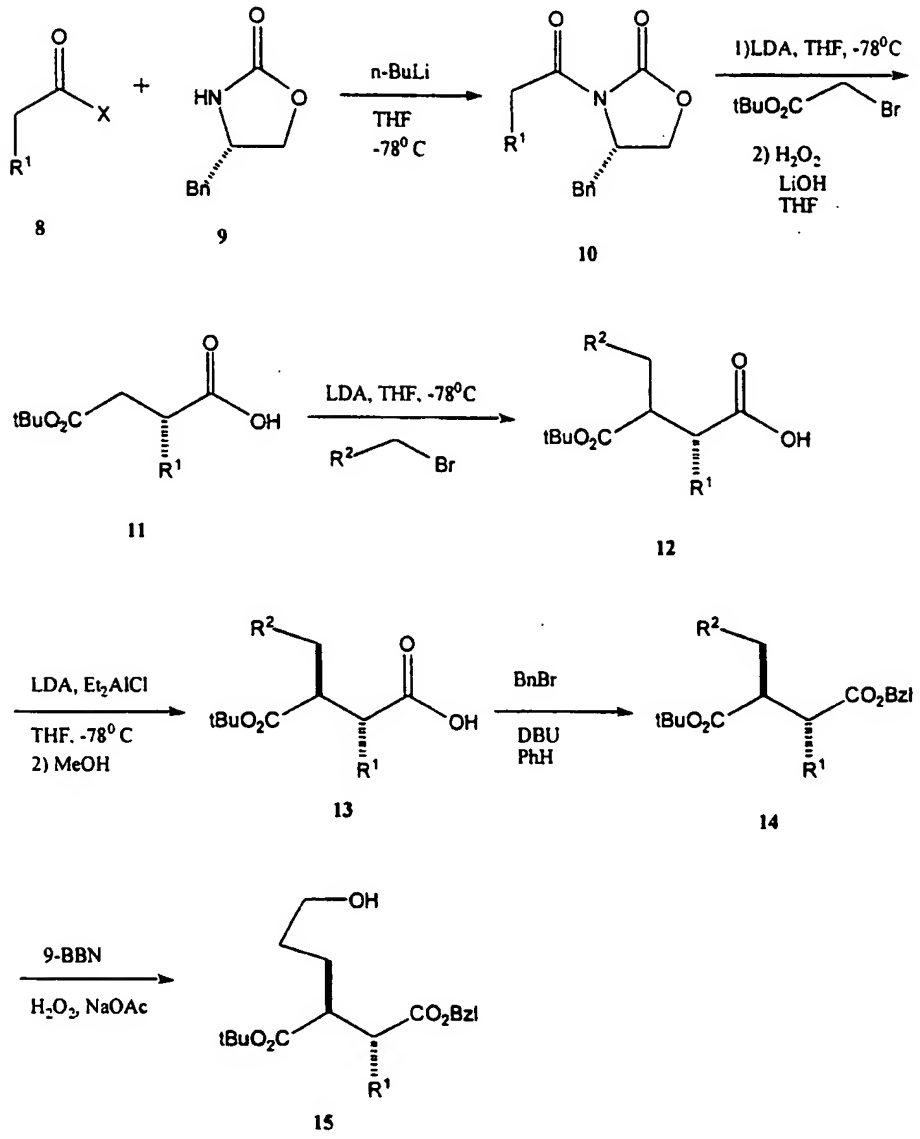
Scheme 1



The synthesis of the 2,3-disubstituted succinic acid portion is described in Scheme 2 below. The acid chloride **8** (X = Cl) is converted to its oxazolidinone derivative **10** using n-butyl lithium. An asymmetric alkylation (JACS, **1982**, 104, 1737) followed by removal of the chiral auxiliary converts **10** to the acid **11**. A second alkylation gives compound **12**. This can be epimerized with LDA and Et_2AlCl to give compound **13**. The benzyl

ester **14** is then made by standard methods. When **14** contains R^2 as an olefin, it can be converted to the alcohol **15** via hydroboration.

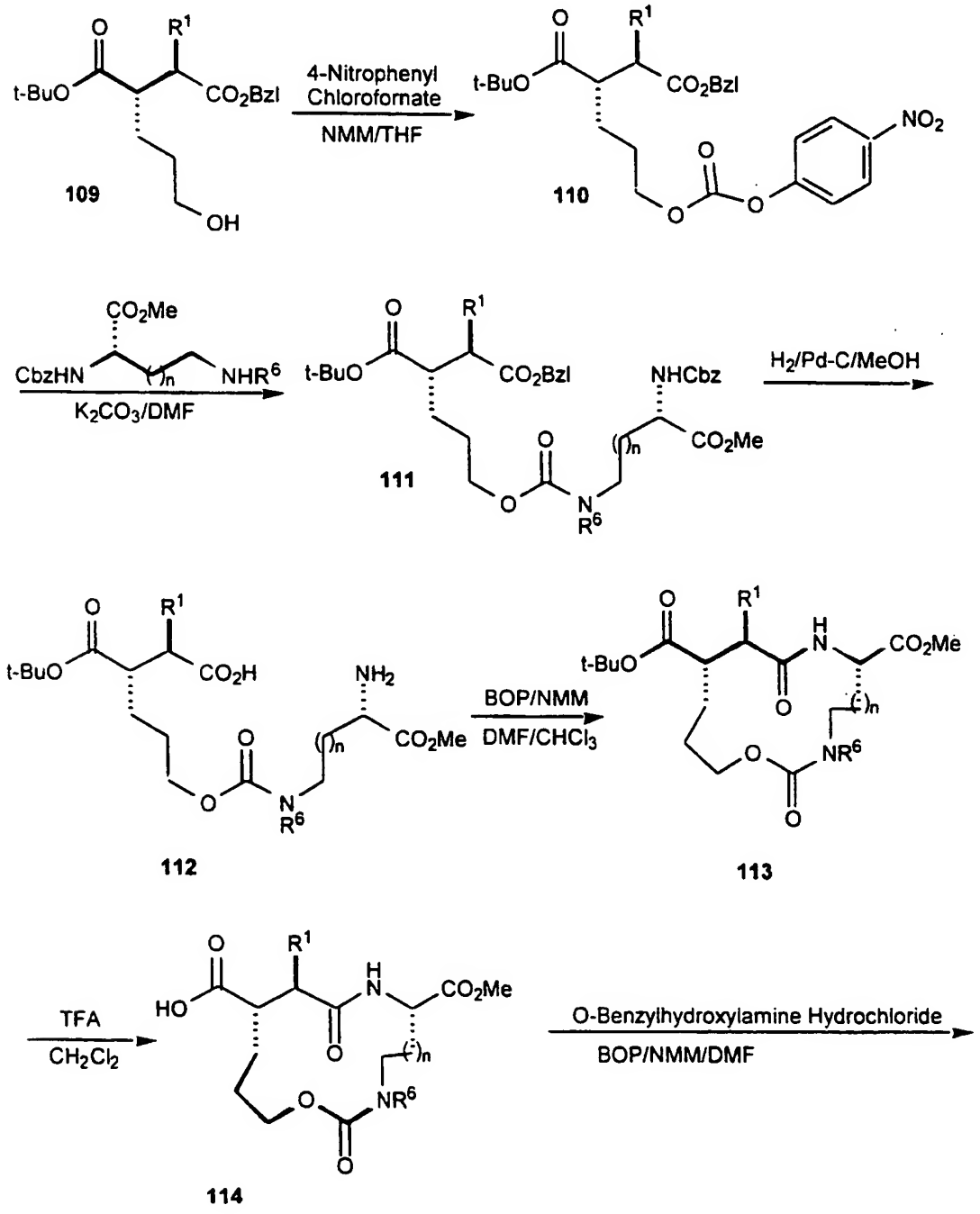
Scheme 2

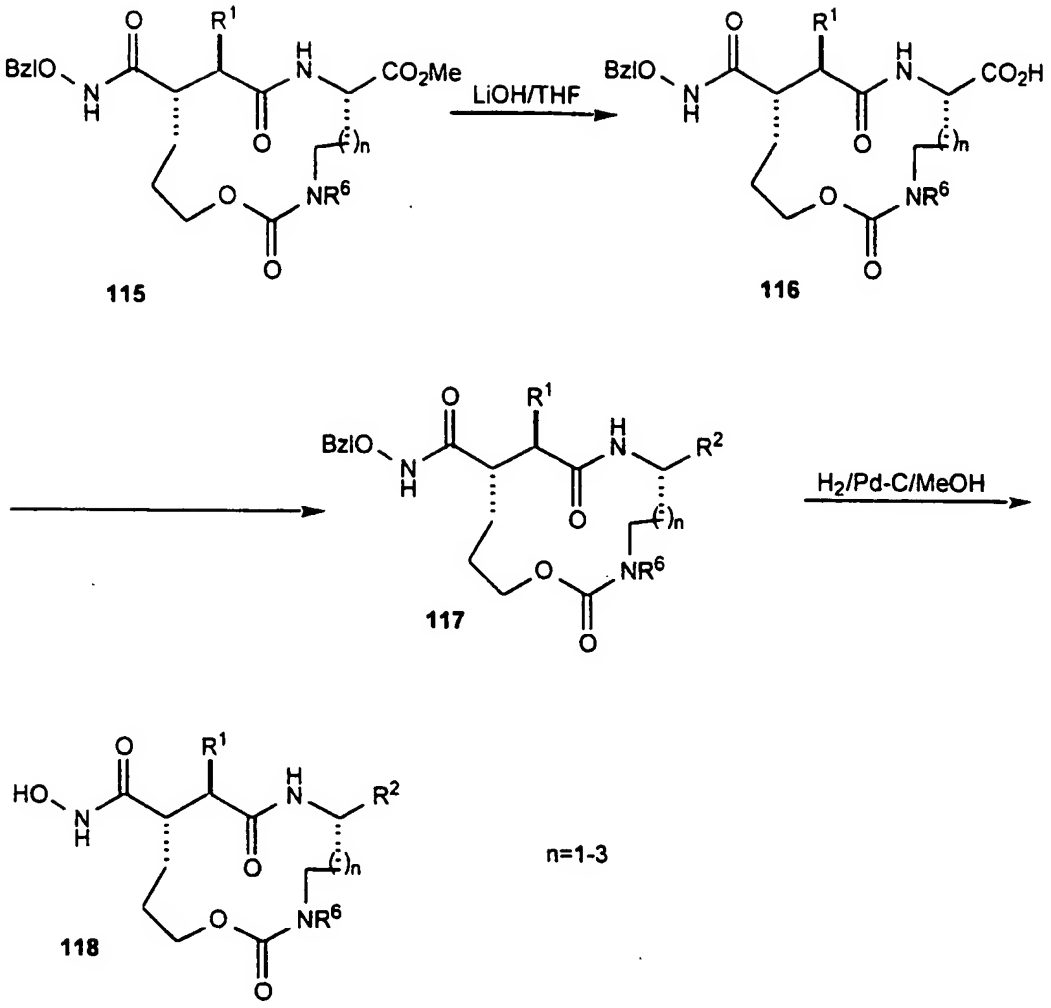


Compounds of formula **118**, where R^2 is an amide or other functionality, can be prepared by the route shown in Scheme 24. The succinate **109** can be converted to the carbonate **110** by 4-nitrophenyl chloroformate. This carbonate **110** reacts with a lysine derivative to yield the carbamate **111**. Hydrogenation gives the amino acid **112**, which is cyclized to give the

macrocycle **113**. The t-butyl ester is converted to the acid **114** using TFA. This material is converted to the O-benzyl hydroxamate **115** via a standard coupling reaction. The methyl ester can be hydrolyzed to the acid and then converted to the desired R^2 group to give **117**. This material is hydrogenated to give the final desired hydroxamate **118**.

Scheme 24





The substituents in the above schemes are defined as follows:

R^1 is isobutyl;

R^2 is defined in Table 32 below; and

R^5 and R^6 are hydrogen.

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of the present invention may be prepared using the reactions and techniques described in this

section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Not all compounds of the present invention falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

Examples

Abbreviations used in the Examples are defined as follows: "1X" for once, "2X" for twice, "3X" for thrice, "bs" for broad singlet, "°C" for degrees Celsius, "Cbz" for benzyloxycarbonyl, "d" for doublet, "dd" for doublet of doublets, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "H" for hydrogen or hydrogens, "^{1}H" for proton, "hr" for hour or hours, "m" for multiplet, "M" for molar, "min" for minute or minutes, "mp" for melting point range, "MHz" for megahertz, "MS" for mass spectroscopy, "nmr" or "NMR" for nuclear magnetic resonance spectroscopy, "t" for triplet, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio. "a", "b", "R" and "S" are stereochemical designations familiar to those skilled in the art.

1(a) 3**R**-Allyl-3-t-Butoxycarbonyl-2(**R**)-isobutyl propanoic acid:

To a stirred cooled(-78 °C) solution of 20 grams (87 mmol) of 3-t-Butoxycarbonyl-2(R)-isobutylpropanoic acid (1.15 g, 5

mmol) (previously aziotroped with toluene) in 400 mL of anhydrous THF, was added 180 mmol of LDA via cannula over 30 minutes. After stirring for 1 hour, 8.3 mL (96 mmol) of allyl bromide was added dropwise. The reaction was allowed to slowly warm to room temperature while stirring overnight. The reaction was quenched with 10% aqueous citric acid followed by removal of the volatiles under reduced pressure. The remaining material was taken into ethyl acetate and washed with H_2O. The aqueous phase was then extracted 3 times with ethyl acetate and the combined organic fractions were washed with 10% citric acid, saturated $NaHCO_3$ (2x), H_2O (2x), and brine then dried over $MgSO_4$. The solvent was removed under reduced pressure obtaining 23.3 grams (99% yield) which was carried on without purification. MS $(M+Na)^+$ = 293

1(b) 3**S**-Allyl-3-t-butoxycarbonyl-2(**R**)-isobutyl propanoic acid:

To a stirred, cooled (-78 °C) solution of 2 grams of acid 1(a) (previously aziotroped 2 times with benzene) in 25 ml of anhydrous THF, was added 16.3 mmol of LDA via cannule over 15 minutes. The reaction was stirred 15 minutes at -78 °C and then for 15 minutes in a room temperature (24 _C) water bath. The reaction was then cooled to -78 °C for 15 minutes, followed by the addition of 15.6 ml of 1 M diethylalluminum chloride (hexane). The reaction was stirred 10 minutes at -78 °C, 15 minutes in a room temperature water bath, then for 15 minutes at -78°C again, followed by quench with the rapid addition of methanol. The reaction mixture was concentrated to ~1/4 its origional volume under reduced pressure and the resulting material was dissolved in 200 ml of ethyl acetate and washed with a mixture of 70 mL of 1N HCl and 100 grams of ice. The aqueous was extracted 2 times with ethyl acetate. The combined organic fractions were washed with a solution of 3.5 grams of KF dissolved in 100 mL of water and 15 mL of 1 N HCl (pH 3-4). The organic phase was washed with brine, dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure affording a 92% mass recovery. ^1H NMR in acetone d-6 indicated an ~8:1 anti syn ratio. MS $(M+Na)^+$ = 293

1(c) Benzyl 3**S**-Allyl-3-t-butoxycarbonyl-2(**R**)-isobutylpropanoate:

To a stirred cooled (0 °C) solution of 20.6 grams(76 mmol) of crude equilibrated acid 1(b) (8:1 mixture) in 75 mL of benzene, was added 11.4 mL (76 mmol) of DBU followed by 9.98 mL (84 mmol) of benzyl bromide. After 10 minutes the reaction was refluxed for 4 hours. The reaction was then diluted to 3 times origional volume with ethyl acetate and washed 3 times with 10% aqueous citric acid. The combined aqueous was extracted 3 times with ethyl acetate. The combined organic fractions were then washed with brine, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The resulting material was chromatographed over silica gel eluting with 2.2 % ethyl acetate/hexanes affording 16.9 grams of benzyl ester (62% yield). MS $(M+NH_4)^+$ = 378

1(d) Benzyl 3**S**-(3-hydroxypropyl)-3-t-butoxycarbonyl-2(**R**)-isobutylpropanoate:

To a stirred, cooled (0 °C) solution of 5.2 grams of olefin 1(c) in 100 mL of anhydrous THF, was added 72.2 mL of 0.5M 9-BBN in THF over 1 hour. The reaction was allowed to warm to room temperature while stirring 12 h. The reaction was cooled to 0 °C followed by the addition of 2.9 mL of H_2O added (caution foaming) dropwise over 5 minutes. After stirring for an additional 20 minutes, 8 mL of H_2O containing 3.21 grams of NaOAc was added simultaneously with 8 mL of 30% H_2O_2 over 5 minutes. The mixture was stirred 20 additional minutes followed by removal of the volatiles under reduced pressure. The remaining material was dissolved in ethyl acetate and washed with brine. The aqueous phase was extracted 2 times with ethyl acetate. The combined organic fractions were washed with water, brine, dried $MgSO_4$ followed by removal of the volatiles under reduced pressure. The resulting material was chromatographed on silica gel with an eluting gradient from 1:20 to 1:10 to 1:5 ethyl acetate/hexanes affording 3.5 grams (64% yield). MS $(M+H)^+$ = 379

Example 869: <u>2**S**,13**S**,14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-7-methyl-2-(N-methylcarboxamido)-cyclopentadecane-13-N-hydroxycarboxamide</u>

869(a). To a solution of the alcohol intermediate 1(d) (11.4 g, 33.1 mmol) and 4-nitrophenyl chloroformate (10.0 g, 50 mmol) in 50 mL CH_2Cl_2 cooled in an ice bath was slowly added N-methylmorpholine (4.4 mL, 40 mmol) and the mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was taken up in 200 mL EtOAc.The solution was washed with brine 3 times, dried ($MgSO_4$) and concentrated. Purification on a silica gel column using 10% EtOAc/hexane gave the desired product (15.0 g, 91%) as a pale yellow solid. DCI-MS: calcd $(M+NH_4)^+$=561; found 561.

869(b). To a solution of 869(a) (15.20 g, 27.28 mmol) and N^a-Cbz-N^d-methyl-L-lysine methyl ester HCl salt (11.22 g, 32.78 mmol) was added potassium carbonate (15 g, 109 mmol) and the mixture was heated at 50 _C for 1 hour. Insoluble material was filtered off and EtOAc was added. The solution was washed with 10% citric acid, brine, $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Purification on a silica gel column using 15% EtOAc/hexane gave an oily product (17.0 g, 91%). ESI-MS: calcd M+1=713.5; found 713.7.

869(c). 869(b) (10.0 g, 14.02 mmol) was dissolved in 30 mL MeOH and the solution was hydrogenated for 1 hour under atmospheric pressure using 10% Pd-C (1.0 g) as catalyst. The catalyst was filtered off and the solution was concentrated to give an oily product (6.8 g, 100%). ESI-MS: calcd M+1=489.4; found 489.6.

869(d). To a solution of BOP (9.2 g, 20.8 mmol) and diisopropylethylamine (12 mL, 70 mmol) in 600 mL $CHCl_3$ cooled in an ice bath was dropwise added a solution of 869(c) (6.8 g, 13.9 mmol) in 50 mL $CHCl_3$ over 2 hours and the mixture was stirred at room temperature overnight. $CHCl_3$ was removed *in vacuo* and EtOAc was added. The solution was washed with 5% citric acid, brine, $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Purification on a silica gel column using 4% MeOH/CH_2Cl_2 gave the cyclic product (3.4 g, 46%) as a powder. ESI-MS: calcd M+1=471.4; found 471.5.

869(e). 869(d) (2.6 g, 5.5 mmol) was treated with 20 mL 50% TFA in CH_2Cl_2 for 1 hour and the solution was concentrated to give an oily product (2.3 g, 100%). ESI-MS: calcd. M+1=415.3; found 415.4.

869(f). To a solution of 869(e) (2.2 g, 5.3 mmol) and O-benzylhydroxylamine hydrochloride (0.96 g, 6.15 mmol) in 10 mL DMF cooled in an ice bath was added Diisopropylethylamine (4.3 mL, 24.6 mmol) followed by BOP (2.72 g, 6.15 mmol) and the solution was allowed to stir overnight. EtOAc was added and the solution was washed with 5% citric acid, brine, NaHCO3 and brine, dried ($MgSO_4$) and concentrated to give a crude product which was washed with ether to give the desired product as a pure solid (2.9 g, 90%). ESI-MS: calcd. M+1=520.5; found 520.5.

869(g). 869(f) (0.5 g, 0.96 mmol) was treated with 5 mL THF and 4 mL 1 N LiOH for 1 hour and the solution was acidified with TFA and concentrated. EtOAc was added and the solution was washed with brine, dried ($MgSO_4$) and concentrated to give the acid as a solid (0.3 g, 63%). ESI-MS: calcd M+1=506.5; found 506.5.

869(h) To a solution of 869(g) (0.2 g, 0.396 mmol) and methylamine hydrochloride (0.11 g, 1.58 mmol) in 2 mL DMF cooled in an ice bath was added BOP (0.18 g, 0.4 mmol) followed by diisopropylethylamine (0.52 mL, 3 mmol). The mixture was allowed to stir at room temperature for 2 hours. EtOAc was added and the product precipitated out. The precipitate was filtered and washed with EtOAc and water to give the title compound as a solid (0.15 g, 73%). ESI-MS: calcd M+1=519.4; found 519.5.

Example 869: 869(h) (120 mg, 0.23 mmol) in 5 mL MeOH was hydrogenated for 30 min at atmospheric pressure using 10% Pd-C (40 mg) as catalyst. The catalyst was filtered off and the solution was concentrated. Purification on reversed phase HPLC afforded the final product as a powder (81 mg, 82%). ESI-MS: calcd M+1=429.3; found 429.4.

Example 2934: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-methylpiperazinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 541.3

Example 2935: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-alanine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 564.3 (M+Na)

Example 2936: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-valine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 592.2 (M+Na)

Example 2937: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-tert-butylglycine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 606.4 (M+Na)

Example 2938: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(b-alanine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 564.3 (M+Na)

Example 2939: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(ethoxycarbonyl-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 580.3 (M+Na)

Example 2940: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-hydroxy-2-phenylethyl)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 543.3 (M+Na)

Example 2941: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-benzylpiperazinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 617.3 (M+1)

Example 2942: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-phenylpiperazinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 616.7 (M+1)

Example 2943: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-(2-pyridyl)piperazinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 604.4(M+1)

Example 2944: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(α-cyclopropanethyloxycarboxamide-β-alanine)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 600.3(M+1)

Example 2945: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[glycine-N-4-(1-piperidinyl)piperidinamide]carboxamide}cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 609.4(M+1)

Example 2946: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(*R*-isopropyloxycarbonyl-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 572.3(M+1)

Example 2947: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(*S*-isopropyloxycarbonyl-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 572.3(M+1)

Example 2948: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-thiazole-4-acetic acid)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 564.2(M+Na)

Example 2949: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(a-cyclopropaneethyloxycarboxamide-b-alanine-N-dimethylamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 627.3(M+1)

Example 2950: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(α-cyclopropaneethyloxycarboxamide-β-alanine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 627.3(M+1)

Example 2951: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-thiazole-4-acetyl-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 611.2(M+1)

Example 2952: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-serine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 558.2(M+1)

Example 2953: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-piperidinamide-3-carboxylic acid)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 592.2(M+Na)

Example 2954: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-2,6-dimethylmorpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 556.4(M+1)

Example 2955: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-ethoxycarbonylpiperazinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 599.4(M+1)

Example 2956: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-ethoxycarbonylpiperidinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 598.4(M+1)

Example 2957: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[4-(1-morpholinyl)phenyl]carboxamide}cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 562.3(M+1)

Example 2958: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[glycine-N-(4-(1-morpholinyl)anilide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 619.4(M+1)

Example 2959: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-piperidinamide-4-carboxylic acid)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 592.3(M+Na)

Example 2960: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-methylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 437(M+Na)

Example 2961: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[alanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 508(M+Na)

Example 2962: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[methylcarboxy]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 438(M+Na)

Example 2963: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[glycine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 494(M+Na)

Example 2964: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-morpholinoethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 514(M+H)

Example 2965: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-morpholinopropylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 528(M+H)

Example 2966: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[pheylalanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 584(M+Na)

Example 2967: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[leucine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 550(M+Na)

Example 2968: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 492(M+H)

Example 2969: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R,S)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 507(M+Na)

Example 2970: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-phenylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 499(M+Na)

Example 2971: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[t-butylglycine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 550(M+Na)

Example 2972: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-benzylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 513(M+Na)

Example 2973: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-(2-oxo-pyrrolidino)propylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 548(M+Na)

Example 2974: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-ethylpyrrolidinocarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 498(M+H)

Example 2975: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-3-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 492(M+H)

Example 2976: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-(1,1,1-trifluoroethyl)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 505(M+Na)

Example 2977: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-(2-pyridyl)ethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 506(M+H)

Example 2978: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R,S-1-methyl-3-pheylpropyl)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 555(M+Na)

Example 2979: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-imidazoylpropylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 509(M+H)

Example 2980: 2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[e-N-t-butyloxycarbonyllysine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 665(M+H)

Example 2981: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[lysine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 543(M+H)

Example 2982: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 492(M+H)

Example 2983: 22**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-N-morpholinocarboxyamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 508(M+Na)

Example 2984: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 507(M+Na)

Example 2985: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2(4-imidazoyl)ethylcarboxyamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 495(M+H)

Example 2986: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-R-(2-R-hydroxyindane)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 555(M+Na)

Example 2987: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-S-(2-S-hydroxyindane)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 555(M+Na)

Example 2988: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-aminobenzylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 504(M-H)

Example 2989: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-piperazinoethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 513(M+H)

Example 2990: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-methylpiperinocarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 498(M+H)

Example 2991: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-(2-R,S-methyl-piperidino)propylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 540(M+H)

Example 2992: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(S)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 507(M+Na)

Example 2993: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[aspartate(O-t-butyl)-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 608(M+Na)

Example 2994: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[aspartate-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 552(M+Na)

Example 2995: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-azaphenylalanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 563(M+H)

Example 2996: 2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-benzhydrylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 589(M+Na)

Example 2997: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine-n-pentyl ester]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 528.6

Example 2998: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-4-phenyl-1-butylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 532.7

Example 2999: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[5-methoxytryptamine]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 573.7

Example 3000: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[1-(2,5-dimethoxyphenyl)-2-glycine amidoethanol]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 637.7

Example 3001: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine-t-butyl ester]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 514.6

Example 3002: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid-a, g -di-t-butyl ester]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 658.8

Example 3003: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 458.5

Example 3004: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-2-phenyl-1-butylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 519.7

Example 3005: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(2-aminoethyl)-1-methylpyrrole]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 507.6

Example 3006: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(2-aminoethyl)benzenesulfonamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 583.7

Example 3007: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid-g-cyclohexyl ester-N-methyl amide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 611.7

Example 3008: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-phenylalanine-p-fluoro-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 579.7

Example 3009: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-phenylalanine-p-methoxy-N-(*S*)-a-methylbenzylamide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 681.8

Example 3010: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-cyclohehylmethyl amide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 496.7

Example 3011: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-3-phenyl-1-propyl amide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 518.7

Example 3012: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-3,3-diphenylpropyl amide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 594.8

Example 3013: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-(2-aminoethylamino)ethyl pyrrolidine]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 654.7

Example 3014: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-3(2'-naphthyl)alanine-N-methyl amide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 611.7

Example 3015: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[ethyl-4-amino-1-piperidine carboxylate]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 555.7

Example 3016: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[5-methyl tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 557.7

Example 3017: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-4-trifluoromethylbenzyl amide]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 558.6

Example 3018: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 546.6

Example 3019: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(diethylamino)ethyl-4-amino benzoate]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 733.8

Example 3020: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[6-fluorotryptamine]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 561.7

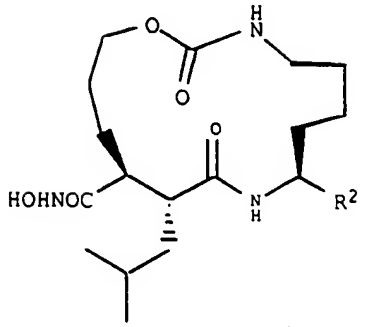
Example 3021: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[6-methoxy tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide

This compound was prepared using the procedures analogous to those above. ESI-MS: 573.7

Example 3022: 2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide

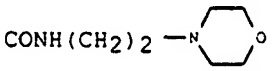
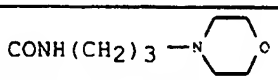
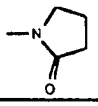
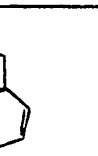
This compound was prepared using the procedures analogous to those above. ESI-MS: 543.7

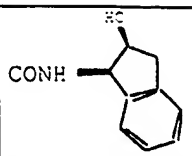
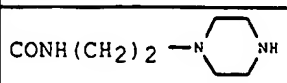
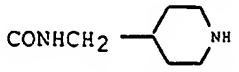
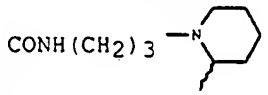
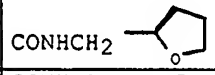
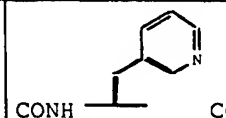
TABLE 32



Ex	R^2	MS (ESI)
2930	$COHCH_2CON$-morphlino	527.6
2931	$CONHCH_2CO$[N-hydroxypiperidine]	541.7
2934	$CONHCH_2CON$-(4-methylpiperazino)	541.3 (M+1)
2935	$CONHCH(CH_3)CON$-morpholino	564.3 (M+1+Na)
2936	CONHCH(isopropyl)CON-morpholino	592.2 (M+1+Na)
2937	CONHCH(tert-butyl)CON-morpholino	606.4 (M+1+Na)
2938	$CONHCH_2CH_2CON$-morpholino	564.3 (M+1+Na)
2939	$CONHCH_2CH_2OCON$-morpholino	580.3 (M+1+Na)
2940	$CONHCH_2CH(OH)Ph$	543.3 (M+1+Na)
2941	$CONHCH_2CON$-(4-benzylpiperazino)	617.3 (M+1)
2942	$CONHCH_2CON$-(4-phenylpiperazino)	603.3 (M+1)
2943	$CONHCH_2CON$-[4-(2-pyridyl)morpholino]	604.4 (M+1)
2944	$CONHCH_2CH$(*S*-$NHCOOCH_2CH_2$-cyclopropane)COOH	600.3 (M+1)
2945	$CONHCH_2CON$-[4-(1-piperidinyl)piperidino]	609.4 (M+1)
2946	$CONHCH_2CH$(*R*-CH_3)OCON-morpholino	572.3 (M+1)
2947	$CONHCH_2CH$(*S*-CH_3)OCON-morpholino	572.3 (M+1)
2948	CONH-2-thiazole-4-acetic acid	564.2 (M+1+Na)
2949	$CONHCH_2CH$(*S*-$NHCOOCH_2CH_2$-cyclopropane)$CON(CH_3)_2$	627.3 (M+1)
2950	$CONHCH_2CH$(*S*-$NHCOOCH_2CH_2$-cyclopropane)CON-morpholino	669.3 (M+1)
2951	CONH-2-thiazole-4-CH_2CON-morpholino	611.2 (M+1)
2952	$CONHCH(CH_2OH)CON$-morpholino	558.2 (M+1)
2953	$CONHCH_2CON$-morpholino-3-carboxylic acid	592.2 (M+1+Na)
2954	$CONHCH_2CON$-(2,6-dimethylmorpholino)	556.4 (M+1)
2955	$CONHCH_2CON$-(4-ethoxycarbonylpiperazino)	599.4 (M+1)
2956	$CONHCH_2CON$-(4-ethoxycarbonylpiperidino)	598.4 (M+1)
2957	CONH-[4-(4-morpholinyl)Ph]	562.3 (M+1)
2958	$CONHCH_2CONH$-[4-(4-morpholinyl)Ph]	619.4 (M+1)

2959	$CONHCH_2CON$-piperidine-4-carboxylic acid	592.3 (M+1+Na)

2960	$CONHCH_3$	$[M+Na]^+=437$
2961	CONH-Ala-$NHCH_3$	$[M+Na]^+=508$
2962	CO_2CH_3	$[M+Na]^+=438$
2963	$CONHCH_2CONHCH_3$	$[M+Na]^+=494$
2964	$CONH(CH_2)_2$ 	$[M+H]^+=514$
2965	$CONH(CH_2)_3$ 	$[M+H]^+=528$
2966	CONH-Phe-$NHCH_3$	$[M+Na]^+=584$
2967	CONH-Leu-$NHCH_3$	$[M+Na]^+=550$
2968	$CONHCH_2$-4-pyridyl	$[M+H]^+=492$
2969	$CONHCH_2$ 	$[M+Na]^+=507$
2970	$CONHC_6H_5$	$[M+Na]^+=499$
2971	CONH-t-butylglycine-$NHCH_3$	$[M+Na]^+=550$
2972	$CONHCH_2C_6H_5$	$[M+Na]^+=513$
2973	$CONH(CH_2)_3$ 	$[M+Na]^+=548$
2974	$CONH(CH_2)_2$ 	$[M+H]^+=498$
2975	$CONHCH_2$-3-pyridyl	$[M+H]^+=492$
2976	$CONHCH_2CF_3$	$[M+Na]^+=505$
2977	$CONH(CH_2)_2$-2-pyridyl	$[M+H]^+=506$
2978	$CONH(\pm)CH(CH_3)CH_2CH_2C_6H_5$	$[M+Na]^+=555$
2979	$CONH(CH_2)_3$ 	$[M+H]^+=509$
2980	CONH-Lys(Boc)-$NHCH_3$	$[M+H]^+=665$
2981	CONH-Lys-$NHCH_3$	$[M+H]^+=543$
2982	$CONHCH_2$-2-pyridyl	$[M+H]^+=492$
2983	CONH 	$[M+Na]^+=508$
2984	$CONHCH_2$ 	$[M+Na]^+=507$
2985	$CONH(CH_2)_2$ 	$[M+H]^+=495$
2986	CONH 	$[M+Na]^+=555$

2987		$[M+Na]^+$=555
2988	$CONHCH_2$-Ph-4-NH_2	$[M-H]^-$=504
2989		$[M+H]^+$=513
2990		$[M+H]^+$=498
2991		$[M+H]^+$=540
2992		$[M+Na]^+$=507
2993	CONH-Asp(t-Bu)-$NHCH_3$	$[M+Na]^+$=608
2994	CONH-Asp-$NHCH_3$	$[M+Na]^+$=552
2995		$[M+H]^+$=563
2996	$CONHCH(C_6H_5)_2$	$[M+Na]^+$=589
2997	$CONHCH_2CO_2C_5H_{11}$	528.6
2998	$CONH(Ch_2)_4Ph$	532.7
2999	$CONH(CH_2)_2$-5-methoxy indole	573.7
3000	$CONHCH_2CONHCH_2CH(OH)$-2,5-dimethoxyphenyl	637.7
3001	$CONHCH_2CO_2tBU$	514.6
3002	$CONHCH(S)(CH_2)_2CO_2tBU(CO_2tBu)$	658.8
3003	$CONHCH_2CO_2H$	458.5
3004	$CONH(CH_2)_2Ph$	519.7
3005	$CONH(CH_2)_2$-1-methylpyrrole	507.6
3006	$CONH(CH_2)_2NHSO_2Ph$	583.7
3007	$CONHCH(S)CH_2CO_2C_6H_{11}(CONHCH_3)$	611.7
3008	$CONHCH(S)CH_2$-p-fluoro-phenyl($CONHCH_3$)	579.7
3009	$CONHCH(S)CH_2$-p-methoxy Ph($CONHCH(S-CH_3)Ph$)	681.8
3010	$CONHCH_2C_6H_{11}$	496.7
3011	$CONH(CH_2)_3Ph$	518.7
3012	$CONH(CH_2)_2CH(Ph)_2$	594.8
3013	$CONH(CH_2)_2NH(CH_2)_2$-pyrrolidine	654.7
3014	$CONHCH(S)CH_2$-2'-naphthyl($CONHCH_3$)	611.7
3015	CONH-piperidine-4-N-$CO_2CH_2CH_3$	555.7
3016	$CONH(CH_2)_2$-5-methylindole	557.7
3017	$CONHCH_2$-p-CF_3-phenyl	558.6
3018	$CONHCH(S)(CH_2)_2CO_2H(CO_2H)$	546.6
3019	CONH-p-Ph-$CO_2CH_2CH_2N(C_2H_5)_2$	733.8
3020	$CONH(CH_2)_2$-6-fluoroindole	561.7
3021	$CONH(CH_2)_2$-6-methoxyindole	573.7

3022	$CONH(CH_2)_2$-indole	543.7

UTILITY

The compounds of the present invention possess metalloproteinase and aggrecanase and TNF inhibitory activity. The MMP-3 inhibitory activity of the compounds of the present invention is demonstrated using assays of MMP-3 activity, for example, using the assay described below for assaying inhibitors of MMP-3 activity. The compounds of the present invention are bioavailable in vivo as demonstrated, for example, using the ex vivo assay described below. The compounds of the present invention have the ability to suppress/inhibit cartilage degradation in vivo, for example, as demonstrated using the animal model of acute cartilage degradation described below.

The compounds provided by this invention are also useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit MPs. These would be provided in commercial kits comprising a compound of this invention.

Metalloproteinases have also been implicated in the degradation of basement membrances to allow infiltration of cancer cells into the circulation and subsequent penetration into other tissues leading to tumor metastasis. (Stetler-Stevenson, Cancer and Metastasis Reviews, 9, 289-303, 1990.) The compounds of the present invention should be useful for the prevention and treatment of invasive tumors by inhibition of this aspect of metastasis.

The compounds of the present invention would also have utility for the prevention and treatment of osteopenia associated with matrixmetalloproteinase-mediated breakdown of cartilage and bone which occurs in osteoporosis patients.

Compounds which inhibit the production or action of TNF and/or Aggrecanase and/or MP's are potentially useful for the treatment or prophylaxis of various inflammatory, infectious, immunological or malignant diseases. These include, but are not limited to inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase response, an acute infection, septic shock, haemodynamic shock and sepsis syndrome, post ischaemic reperfusion injury, malaria, Crohn's disease, mycobacterial infection, meningitis, psoriasis, periodontits, gingivitis, congestive heart failure, fibrotic disease,

cachexia, and aneroxia, graft rejection, cancer, corneal ulceration or tumor invasion by secondary metastases, autoimmune disease, skin inflammatory diseases, multiple osteo and rheumatoid arthritis, multiple sclerosis, radiation damage, HIV, and hyperoxic alveolar injury.

The compounds of the present invention have been shown to inhibit TNF production in lipopolysacharride stimulated mice, for example, using the assay for TNF Induction in Mice and in human whole blood asdescribed below.

The compounds of the present invention have been shown to inhibit aggrecanase a key enzyme in cartilage breakdown as determined by the aggrecanase assay described below.

As used herein "µg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "µL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "µM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

A compound is considered to be active if it has an IC_{50} or K_i value of less than about 1 mM for the inhibition of MMP-3.

Aggrecanase Enzymatic Assay

A novel enzymatic assay was developed to detect potential inhibitors of aggrecanase. The assay uses active aggrecanase accumulated in media from stimulated bovine nasal cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate.

The substrate concentration, amount of aggrecanase time of incubation and amount of product loaded for Western analysis were optimized for use of this assay in screening putative aggrecanase inhibitors. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF_) or other stimuli. Matrix metalloproteinases (MMPs) are secreted from cartilage in an inactive, zymogen form following stimulation, although active enzymes are present within the matrix. We have shown that following depletion of the extracellular aggrecan matrix, active MMPs are released into the culture media. (Tortorella, M.D. et. al. Trans. Ortho. Res. Soc. 20, 341, 1995). Therefore, in order to accumulate BNC

aggrecanase in culture media, cartilage is first depleted of endogenous aggrecan by stimulation with 500 ng/ml human recombinant IL-ß for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. In order to decrease the amounts of other matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media, containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes, CE, et al., Biochem J 306:799-804, 1995). This antibody recognizes aggrecan fragments with the N-terminus, 374ARGSVIL.., generated upon cleavage by aggrecanase. The BC-3 antibody recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein core. Other proteases produced by cartilage in response to IL-1 do not cleave aggrecan at the Glu373-Ala374 aggrecanase site; therefore, only products produced upon cleavage by aggrecanase are detected. Kinetic studies using this assay yield a Km of 1.5 +/- 0.35 uM for aggrecanase.

To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water or other solvents and diluted to appropriate concentrations in water. Drug (50 ul) is added to 50 ul of aggrecanase-containing media and 50 ul of 2 mg/ml aggrecan substrate and brought to a final volume of 200 ul in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM CaCl2. The assay is run for 4 hr at 37oC, quenched with 20 mM EDTA and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background.

Removal of the glycosaminoglycan side chains from aggrecan is necessary for the BC-3 antibody to recognize the ARGSVIL

epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 ug GAG) for 2 hr at 37oC and then with keratanase (0.1 units/10 ug GAG) and keratanase II (0.002 units/10 ug GAG) for 2 hr at 37oC in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 ul of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

Bisacetylated Substance P / MMP-3 fluorescent Assay

A high capacity enzymatic assay was developed to detect potential inhibitors of MMP-3. The assay uses a derivative of a peptide substrate, substance P (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met), which is cleaved by MMP-3 exclusively at the glutamine-phenylalanine bond. In order to adapt this assay for high throughput screening, we have developed a fluorimetric method of product detection. The production of the hydrolysis product, substance P 7-11, is measured by reaction with fluorescamine, a fluorogenic compound which reacts with the primary amine of this fragment. The substance P substrate is bisacetylated to block the primary amines of the intact substrate. Thus, the resulting fluorescence represents generation of product (7-11 peptide) formed upon cleavage by MMP-3, and is quantitated using a standard curve prepared with known concentrations of 7-11 peptide. Kinetic studies using the bisacetylated substrate yield the following parameters for MMP-

3: Km =769 +/- 52 uM; Vmax = 0.090 +/- 0.003 nmoles 7-11 peptide/min.

To evaluate inhibition of MMP-3, compounds were prepared at a concentration of 10 mM in 100% methanol, and then further diluted to a 20X molar stock. Five microliters of each drug stock was added to the assay in the presence of 20 nM truncated MMP-3 in 67.5 mM tricine (pH 7.5), 10 mM $CaCl_2$, 40 mM NaCl, and 0.005% Brij 35 in a final volume of 100 microliters. Bisacetylated substance P (1000 mM) was added, and the assay was run for 1 hour at 25°C. The reaction was quenched with EDTA (20 mM) and product was detected fluorometrically following addition of fluorescamine (0.075 mg/ml). Fluorescence of each sample was converted to an amount of product formed using a substance P 7-11 standard curve. Under these conditions, the assay is linear with respect to MMP-3 amount up to 10 pmoles. Inhibition of MMP-3 was determined by comparing the amount of product generated in the presence and absence of compound.

Selected compounds of the present invention were tested and shown to have activity in the above assay.

Ex vivo assay for bioavailability of MMP-3 inhibitors

Blood was collected by cardiac puncture from rats at different times after dosing I.V., I.P., or P.O. with compound in order to determine the levels of inhibitor present. Plasma was extracted with 10% TCA in 95% methanol, and placed on ice for 10 minutes. The plasma was then centrifuged for 15 minutes at 14,000 rpm in an Eppendorf microcentrifuge. The supernatant was removed, recentrifuged, and the resulting supernatant was diluted 1:10 in 50 mM tricine, pH 8.5. The pH of the sample was adjusted to 7.5, and then assayed in the MMP-3 substance P fluorescent enzymatic assay. Plasma from naive rats was extracted by the same method and used as a negative control. This plasma was also used to prepare a spiked plasma curve of the compound of interest. Known concentrations of the compound were added to control plasma, the plasma was extracted by the same method, and then assayed in the MMP-3 enzymatic assay. A standard curve was prepared that related percent inhbition in the MMP-3 assay to the concentration of drug added in the spiked

samples. Based on the percent inhibition in the presence of plasma from dosed rats, the concentration of compound was determined using the standard curve.

Acute Cartilage Degradation Rat Model

A novel in vivo model of acute cartilage degradation in rats has been characterized as a method to determine the proteoglycan content in the synovial fluid after the induction of cartilage degradation. Experimental groups exhibit increased levels of proteoglycan content in their synovial fluid versus control rats. The criteria to demonstrate a compound's activity in this model, is the ability to inhibit the demonstration of cartilage degradation, as measured by increased proteoglycan content in the synovial fluid of rats after compound administration. Indomethacin, a non-steroidal anti-inflammatory drug is inactive in this model. Indomethacin administration does not inhibit the demonstration of cartilage degradation in experimental animals. In contrast, administration of a compound of this invention significantly inhibited the demonstration of cartilage degradation in this model.

TNF Human Whole Blood Assay

Blood is drawn from normal donors into tubes containing 143 USP units of heparin/10ml. 225ul of blood is plated directly into sterile polypropylene tubes. Compounds are diluted in DMSO/serum free media and added to the blood samples so the final concentration of compounds are 50,10,5,1,.5,.1, and .01uM. The final concentration of DMSO does not exceed .5%. Compounds are preincubated for 15 minutes before the addition of 100ng/ml LPS. Plates are incubated for 5 hours in an atmosphere of 5% CO2 in air. At the end of 5 hours, 750ul of serum free media is added to each tube and the samples are spun at 1200RPM for 10 minutes. The supernatant is collected off the top and assayed for TNF-alpha production by a standard sandwich ELISA. The ability of compounds to inhibit TNF-alpha production by 50% compared to DMSO treated cultures is given by the IC50 value.

TNF Induction In Mice

Test compounds are administered to mice either I.P. or P.O. at time zero. Immediately following compound administration, mice receive an I.P. injection of 20 mg of D-galactosamine plus 10 µg of lipopolysaccharide. One hour later, animals are anesthetized and bled by cardiac puncture. Blood plasma is evaluated for TNF levels by an ELISA specific for mouse TNF. Administration of representative compounds of the present invention to mice results in a dose-dependent suppression of plasma TNF levels at one hour in the above assay.

Dosage and Formulation

The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, Mack Publishing.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiinflammatory and antiarthritic agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action, MMP-3, in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents.

They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches wall known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable

pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class

of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition,

parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

Capsules are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 100 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of unit capsules may also prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Syrup

	Wt. %
Active Ingredient	10
Liquid Sugar	50
Sorbitol	20
Glycerine	5
Flavor, Colorant and Preservative	as required
Water	as required

The final volume is brought up to 100% by the addition of distilled water.

Aqueous Suspension

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.01
Keltrol® (Food Grade Xanthan Gum)	0.2
Liquid Sugar	5
Flavor, Colorant and Preservative	as required
Water	as required

Xanthan gum is slowly added into distilled water before adding the active ingredient and the rest of

the formulation ingredients. The final suspension is passed through a homogenizer to assure the elegance of the final products.

Resuspendable Powder

	Wt. %
Active Ingredient	50.0
Lactose	35.0
Sugar	10.0
Acacia	4.7
Sodium Carboxylmethylcellulose	0.3

Each ingredient is finely pulverized and then uniformly mixed together. Alternatively, the powder can be prepared as a suspension and then spray dried.

Semi-Solid Gel

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.02
Gelatin	2
Flavor, Colorant and Preservative	as required
Water	as required

Gelatin is prepared in hot water. The finely pulverized active ingredient is suspended in the gelatin solution and then the rest of the ingredients are mixed in. The suspension is filled into a suitable packaging container and cooled down to form the gel.

Semi-Solid Paste

	Wt. %
Active Ingredient	10
Gelcarin® (Carrageenin gum)	1
Sodium Saccharin	0.01
Gelatin	2
Flavor, Colorant and Preservative	as required
Water	as required

Gelcarin® is dissolved in hot water (around 80°C) and then the fine-powder active ingredient is suspended in this solution. Sodium saccharin and the rest of the formulation ingredients are added to the suspension while it is still warm. The suspension is homogenized and then filled into suitable containers.

Emulsifiable Paste

	Wt. %
Active Ingredient	30
Tween® 80 and Span® 80	6
Keltrol®	0.5
Mineral Oil	63.5

All the ingredients are carefully mixed together to make a homogenous paste.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of tablets may also be prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely divided active

ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be administered in combination with a second therapeutic agent, especially non-steroidal anti-inflammatory drugs (NSAID's). The compound of the present invention and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of the present invention may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of the present invention and the second therapeutic agent are not formulated together in a single dosage unit, the compound of the present invention and the second therapeutic agent may be administered essentially at the same time, or in any order; for example the compound of the present invention may be administered first, followed by administration of the second agent. When not administered at the same time, preferably the administration of the compound of the present invention and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

Preferably the route of administration of the compound of the present invention is oral. Although it is preferable that the compound of the present invention and the second therapeutic agent are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of the present invention when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind

of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of

osteoarthritis or rheumatoid arthritis, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

CLAIMS

WHAT IS CLAIMED:

1. A compound, and pharmaceutically acceptable salt forms thereof, selected from:

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine-n-pentyl ester]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-4-phenyl-1-butylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[5-methoxytryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[1-(2,5-dimethoxyphenyl)-2-glycine amidoethanol]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine-t-butyl ester]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid-a, g -di-t-butyl ester]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[glycine]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-2-phenyl-1-butylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(2-aminoethyl)-1-methylpyrrole]-cyclopentadecane-13-N-hydroxycarboxamide;

2***S***, 13***S***, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(2-aminoethyl)benzenesulphonamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid-g-cyclohexyl ester-N-methyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-phenylalanine-p-fluoro-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-phenylalanine-p-methoxy-N-(*S*)-a-methylbenzylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-cyclohehylmethyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-3-phenyl-1-propyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-3,3-diphenylpropyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-(2-aminoethylamino)ethyl pyrrolidine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-3(2'-naphthyl)alanine-N-methyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[ethyl-4-amino-1-piperidine carboxylate]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[5-methyl tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[N-4-trifluoromethylbenzyl amide]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[L-glutamic acid]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[2-(diethylamino)ethyl-4-amino benzoate]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[6-fluorotryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[6-methoxy tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2*S*, 13*S*, 14**R**-1, 7-diaza-8, 15-dioxo-9-oxa-14-isobutyl-2[tryptamine]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-methylpiperazinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-alanine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-valine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-tert-butylglycine-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(b-alanine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(ethoxycarbonyl-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-hydroxy-2-phenylethyl)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-benzylpiperazinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-phenylpiperazinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-(2-pyridyl)piperazinamide) carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(a-cyclopropaneethyloxycarboxamide-b-alanine)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[glycine-N-4-(1-piperidinyl)piperidinamide]carboxamide} cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(*R*-isopropyloxycarbonyl-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(*S*-isopropyloxycarbonyl-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-thiazole-4-acetic acid)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(a-cyclopropaneethyloxycarboxamide-b-alanine-N-dimethylamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(a-cyclopropaneethyloxycarboxamide-b-alanine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(2-thiazole-4-acetyl-N-morpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(L-serine-N-morpholinamide)carboxamide]cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-piperidinamide-3-carboxylic acid)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-2,6-dimethylmorpholinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-ethoxycarbonylpiperazinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-4-ethoxycarbonylpiperidinamide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[4-(1-morpholinyl)phenyl]carboxamide}cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-{N-[glycine-N-(4-(1-morpholinyl)anilide)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(glycine-N-piperidinamide-4-carboxylic acid)carboxamide] cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-methylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[alanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[methylcarboxy]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[glycine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-morpholinoethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-morpholinopropylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[pheylalanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[leucine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R,S)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-phenylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[t-butylglycine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-benzylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-(2-oxo-pyrrolidino)propylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-ethylpyrrolidinocarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-3-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-(1,1,1-trifluoroethyl)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-(2-pyridyl)ethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R,S-i-methyl -3-pheylpropyl)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-imidazoylpropylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[e-N-t-butyloxycarbonyllysine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[lysine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2-pyridylmethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

22**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-N-morpholinocarboxyamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(R)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-2(4-imidazoyl)ethylcarboxyamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-R-(2-R-hydroxyindane)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2**S**, 13**S**, 14**R**-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-S-(2-S-hydroxyindane)carboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-aminobenzylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[2-N-piperazinoethylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-4-methylpiperinocarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-N-(2-R,S-methyl-piperidino)propylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-(S)-furfurylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[aspartate(O-t-butyl)-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[aspartate-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide;

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[3-azaphenylalanine-N-methylamide]-cyclopentadecane-13-N-hydroxycarboxamide; and

2S, 13S, 14R-1,7-diaza-8,15-dioxo-9-oxa-14-isobutyl-2-[N-benzhydrylcarboxamide]-cyclopentadecane-13-N-hydroxycarboxamide.

2. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

3. A method of treating an inflammatory disease in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

4. A method of treating a condition or disease mediated by MMPs and/or TNF and/or aggrecanase in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

5. A method of treating a condition or disease wherein the disease or condition is referred to as rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, multiple sclerosis, or psoriasis in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

6. A method of treating a condition or disease wherein the disease or condition is referred to as fever, cardiovascular effects, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease or HIV infection in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

7. An assay for detecting inhibitors of aggrecanase, which comprises:

(a) generating soluble aggrecanase, by stimulation of cartilage slices;

(b) detecting aggrecanase enzymatic activity by using the soluble aggrecanase generated in (a) and monitoring production of aggrecan fragments containing the end terminus ARGSVIL;

(c) evaluating inhibition of aggrecanase by comparing the amount of product produced in the presence versus absence of compound.

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C07D 273/02, 413/12, 417/12, 413/14, A61K 31/395, C12Q 1/37

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(71) Applicant: DUPONT PHARMACEUTICALS COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

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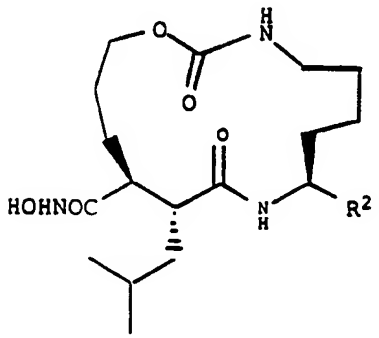

(I)

(57) Abstract

This invention relates to macrocyclic molecules of formula (I) which inhibit metalloproteinases, including aggrecanase, and the production of tumor necrosis factor (TNF). The present invention also relates to pharmaceutical compositions comprising such compounds and to methods of using these compounds for the treatment of inflammatory diseases. A novel enzymatic assay was developed to detect potential inhibitors of aggrecanase. The assay uses active aggrecanase accumulated in media from stimulated bovine nasal cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/09789

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D273/02 C07D413/12 C07D417/12 C07D413/14 A61K31/395 C12Q1/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 13831 A (BRITISH BIO-TECHNOLOGY LIMITED) 20 August 1992 cited in the application see the whole document ---	1-6
A	KSANDER G M ET AL.: "Ortho-substituted benzofused macrocyclic lactams as zinc metalloprotease inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 4, 14 February 1997, pages 495-505, XP002074845 Washington DC, US see the whole document ---	1-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 August 1998	03. 11. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ALLARD, M

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INTERNATIONAL SEARCH REPORT

... ernational Application No
PCT/US 98/09789

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 18207 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 22 May 1997 see the whole document, particularly claim 9, formula IVd, page 59, third compound, page 195, examples 2930 and 2931, and page 275, table 32	1-6

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/09789

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3-6
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 3-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-6
2. Claims: 7

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. .ational Application No
PCT/US 98/09789

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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